CORTICOSTEROID-INDUCED PARTURITION IN DOMESTIC ANIMALS

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Between 1967 and 1972, research groups in the U.S. (1–9), South Africa (10–16), and Europe (17–33) reported an unexpected effect of some glucocorticosteroids on gestation in ruminants. They induced precocious or premature parturition in the third trimester of pregnancy in cattle, and in the last weeks of gestation in sheep. Consequently, the following questions were raised:

Is this corticosteroid (corticoid) effect a pharmacological effect only, or does it mimic physiological conditions; what is the mechanism of action; would this discovery provide new leads for a better understanding of mechanisms of parturition; is this effect restricted to sheep and cattle, or is the assumption correctly made—for example by the U.S. Food and Drug Administration[1]—that corticoids may endanger the last trimester of gestation in all animals? Furthermore, is the corticoid effect observed in cattle and sheep reliable enough to induce parturition at a predetermined time? This would convert an undesirable physiological effect into a practical farm use for the corticoid. Finally, are there hormonal antagonists available to offset this particular corticoid effect when used in late pregnancy for therapeutic purposes for disease conditions?

This review attempts to answer these and related questions, on the basis of information gathered from the expanding body of knowledge about endocrine functions during late gestation, and those events preceding and initiating parturition in animal and man.

1. The Physiological Role of the Fetal Adrenal in Initiating Parturition in Cattle, Sheep, and Man

As early as 1957, research by Kennedy, Kendrick & Stormont (34), and later by Holm, Parker & Galligan (35), Holm (36), Kennedy, Liggins & Holm (37), Liggins, Kennedy & Holm (38), Drost & Holm (39), and Liggins (40, 41) disclosed that in cattle and sheep a functional hypothalamic-pituitary-adrenal axis in the fetus is a prerequisite for normal parturition after a gestation period of 280 (273–288) days in cattle and 147 (140–152) days in sheep.

[1] By specific request of FDA, all corticoids sold in the USA have to carry the following warning on their labels: "Warning: Clinical and experimental data have demonstrated that corticosteroids administered orally or parenterally to animals may induce the first stage of parturition when administered during the last trimester of pregnancy and may precipitate premature parturition followed by dystocia, fetal death, retained placenta, and metritis."

Delayed parturition is caused in cattle by adenohypophysial aplasia, an inherited defect in Guernsey cattle (34), causing secondary adrenal hypoplasia; or an inherited adrenal defect in Holsteins (42), resulting in poorly developed or undifferentiated adrenals.

In the ewe, cauterization of the fetal hypothalamus, or the hypophysial stalk, or the hypophysis (38), or bilateral adrenalectomy (39), caused prolonged gestation. It has long been recognized that pregnant ewes kept on ranges in the Western U.S. occasionally produce cyclopic fetuses, a congenital anomaly always causing prolonged gestation (43–45). In 1963, Binns, James, Shupe & Everett (45) experimentally produced this malformation, resulting in delayed parturition, by feeding *Veratrum californicum* Durand (Western false hellebore) to pregnant ewes on day 14 of gestation. In 1972, Van Kampen & Ellis (46) reported the same effect from the steroid alkaloids jervin, cyclopamine, and cycloposine, extracted from *Veratrum californicum* Durand: if ingested on day 14 of gestation, the cyclopic anomaly is induced. This anomaly induces absence of the hypophysial stalk and the pituitary, adrenal hypoplasia, and insufficiency as far as steroid production and metabolism is concerned, and prolonged gestation (43–46).

Stimulation of the developing hypothalamic-pituitary-adrenal system by treating the sheep fetus with ACTH during the last trimester of gestation (12, 40, 47–50), or its stimulation by either giving small glucocorticoid doses directly to the fetus (11, 12, 40, 41, 47–51), or much larger doses to the mother late in the gestation period (1–33), confirmed the existence of a parturition-inducing system in sheep with the fetus playing a key role. Van Rensburg (12, 52, 53) demonstrated that abortion in the Angora goat was due to fetal adrenal hyperplasia.

In cattle and sheep, the end of the gestation period and the onset of parturition are characterized either by a dramatic rise in the corticoid blood level in the fetus (lamb: 54; calf: 55), or in the corticoid level of the pregnant cow (3, 27, 56).

Against this background, the pregnancy-terminating effect of exogenous glucocorticosteroids, originally observed during corticoid-therapy in cows late in pregnancy, was not surprising. It could be interpreted as a premature substitute for a signal which normally comes from the fetal adrenal. In general terms, the substitute signal conveys to the maternal organism the information that the fetal hypothalamic-pituitary-adrenal axis has matured, and that the fetus is ready to take the stress of life, and hence that its role as an intra-uterine parasite should be terminated.

Similar conditions may exist in man: anencephaly (which, according to Kalter, 57, is a misnomer for absence of the brain in neonates in that medulla or dysplastic vestiges usually are present), when not accompanied with hydroamnion, can cause delayed parturition (58–64) if the remnants of the pituitary and the hypothalamus are insufficient to stimulate adrenal growth and function (62). Anencephaly plus hydroamnion shortens gestation length (60–62).

Many infants born as a result of "unexplained" premature labor after the 20th week have hyperplasia of the adrenals, which is not seen in infants at a similar gestation age delivered because of specific complications of pregnancy or as a result of therapeutic abortion (62).

2. Corticosteroid-Induced Parturition: Species Differences, Active Compounds, and Mechanism of Action

Corticoid-induced parturition is either precocious or premature termination of gestation as a result of administration of an exogenous corticoid to the maternal compartment of the pregnant animal. Precocious parturition is the delivery one to two weeks early of a fully developed fetus, which does not need special care and has excellent chances of survival. Premature parturition is the delivery of a live fetus during the last trimester of the gestation period; the fetus needs special care when born early.

The present state of published evidence for corticoid-induced parturition is summarized in Table 1.

TABLE 1. Corticosteroid*-Induced Premature or Precocious Parturitions in Mammals.

Species	Induction of Parturition with Corticoids	Phase of Gestation (Treatment Period)	Comment
Cattle (Bos taurus & bos indicus)	+	3rd trimester	Increasing sensitivity to corticosteroids toward term.
Sheep	+	last 2–3 weeks of the gestation period.	ACTH, or corticosteroids, applied to the fetal compartment, are active throughout the 3rd trimester.
Goat	+		
Swine	−	4th quarter	
Horse	−	1st & 3rd trimester	
Dog	−		Detailed investigations are missing.
Rabbit	+	on day 25 (27) only	Insensitive before and after day 25 (27).
Man	?		No treatments reported. Fetal adrenal hypoplasia results in delayed parturition.

* Exogenous corticoids applied to the material compartment.

(*a*) *Species differences* (*Table 1*).—In *cattle*, throughout the last trimester of the gestation period, some, but not all corticoids tested (see Table 2) induce premature or precocious parturition. Details about experimental and field experiences have been reviewed recently (65). Pregnant animals seem to become increasingly sensitive to this corticoid effect towards the end of the gestation period: precocious parturition can be induced with lower doses, higher reliability, and less side effects than premature parturition (65). In *sheep*, by corticoid treatment to the maternal compartment during the last 2–3 weeks of gestation, only precocious parturition can be induced (Table 1). Premature parturition can be provoked only by corticoid (11, 12, 40, 41, 47–51), or ACTH (12, 40, 47–51) application to the fetal compartment. Again, not all compounds tested are efficacious (Table 2). In *goats*, the maternal organism becomes sensitive, as in sheep, only during the last two weeks of gestation (12). However, even high corticoid doses do not always seem to initiate parturition as expected (66). *Sows* seem to be unresponsive to corticoids in late gestation. From our own experiments (65) and others (67) it seems likely that swine do not respond because either the mechanisms operating in the ruminants are absent, or the dose levels employed were not high enough for the termination of gestation. In *horses*, contrary to frequently-voiced opinions of practicing veterinarians, published evidence strongly indicates no effects of corticoids on parturition (3, 68, 69). In *dogs*, clinical observations indicate that corticoids applied during the second half of pregnancy have no effect (70). *Rabbits* seem to respond to corticoids with precocious parturition only when treated on days 25 (71) or 27 (2). Published clinical observations in man on the effects of glucocorticoids applied to mothers during gestation, focus on teratogenetic (71a), abortion (71a, 71b, 71c), and stillbirth (71b, 71c,) inducing activities. A premature or precocious gestation terminating effect has not been reported, nor can it be found in the published case reports (71a, 71b).

(*b*) *Active compounds* (*Table 2*).—From all studies reported, the conclusion can be drawn that only certain glucocorticoids, but none of the mineralocorticoids, can induce parturition. In *cattle*, corticoids active in this respect have been reviewed recently (65). Table 2 gives a breakdown of tested, active as well as inactive, compounds. Three features emerge from these data:

(*i*) All compounds effective in this respect are highly active corticoids, which are now widely used in veterinary medicine. The doses inducing precocious parturition partially overlap with recommended therapeutic doses (Table 2). For inducing premature parturition, maximum therapeutic doses (dexamethasone, triamcinolone) or twice recommended levels (flumethasone) are required.

(*ii*) The efficacious compounds share substitutions in the 16α position (hydroxy or methyl groups: see Table 2). 9α-Fluoro-prednisolone, lacking a 16α substitute, but being therapeutically as active as dexamethasone, seems to be ineffective as parturition inducer (7).

(*iii*) According to investigators in New Zealand (72), where economic and management conditions make the widespread use of premature termination of gestation highly desirable (see page 43), an unusual pattern emerged: so-called

TABLE 2. Corticosteroid-Induced Parturition in Ruminants: Compounds Used and Dose Levels of Efficacious Compounds.

Species	Compound Used	Effective Dose (mg)	Highest Ineffective Dose (mg)	Therapeutic Dose Range (mg)	Route of Application	Days Between Maternal Treatment and Parturition	References
Cattle	Hydrocortisone	—	260	200	i.m.	- -	7
	Prednisolone	- -	200	100	i.m.	—	4
	9α-Fluoroprednisolone acetate	·	80	20	i.m.	—	7
	Dexamethasone[1] (ester or free alcohol)	10–20		10–20	i.m., s.c. intramammary	1–5	1–3, 6, 9, 22, 23–25, 30
	Dexamethasone[1] (ester)*	20	—	10–20	i.m.	10–15	72
	Triamcinolone[2]*	30	—	15–30	i.m.	10–15	72
	Flumethasone[3] (solution)	5–10		2.25–5	i.m.	1–5	4–8, 17–19, 21, 26, 27, 33, 65
	Flumethasone[3] (granulate)	10	7.5	2.5–5	oral	2–5	21, 65
	Flumethasone[3] (suspension)	10	—	5	i.m.	10–15	72
Sheep	Cortisol acetate	—	100	- -	i.m.	—	12, 40
	Cortisol hemisuccinate	—	50–100	·	i.m.	—	40
	Betamethasone[4]	—	20	5	i.m.	—	73
	Dexamethasone[1]	4–25	—	5	i.m.	2	3, 12, 20, 28, 29, 31, 32
	Flumethasone[3] (solution)	0.5–3.0	·	1	i.m.	2–3	13–16

[1] 9α-fluoro-16α-methyl prednisolone
[2] 9α-fluoro-16α-hydroxy prednisolone
[3] 6α,9α-difluoro-16α-methyl prednisolone
[4] 9α-fluoro-16β-methyl prednisolone
* New Zealand studies (see page 43)

"short-acting" corticoids (like flumethasone solution) trigger precocious or premature parturition within the expected time period of 1–5 days; whereas "long-acting" steroid preparations (like flumethasone in suspension, dexamethasone pivalate suspension, and triamcinolone in suspension) caused delayed, but clearly premature parturition, within 10–15 days. The latter method is thought to be advantageous since it carries a lower incidence of retained placenta, an undesirable side-effect, but results in a significantly higher stillbirth rate (see page 43).

In *sheep*, the highly active, 16α substituted compounds (like dexamethasone and flumethasone) are efficacious (Table 2). Interestingly, betamethasone, the 16β methyl analog of dexamethasone, seems to be ineffective, as is cortisol acetate (41, 73), which only becomes active (at 25 mg after day 140) in ewes whose fetuses have been adrenalectomized. In the *goat*, 7 daily doses of 100 mg cortisol acetate (day 113–120), or a single dose of 240 mg (270) methylprednisolone acetate on days 111 or 125, terminated gestation (12); dexamethasone (5 mg) was not consistent in its effect during the last 2 weeks of gestation (66). In *horses*, 10–40 mg dexamethasone given daily for 5 days (3) between days 40–60 of gestation; 20 mg dexamethasone, with 2 or more injections in 5 Shetland ponies during the last two months of gestation (68); 20–40 mg and 10–80 mg (69) during the last month of gestation, all were unsuccessful, and had no adverse effect on fetal life at parturition at term. In the *rabbit*, either 4.0 mg dexamethasone on day 25 (71), or 0.5–1.2 mg on day 27 (2), terminated gestation. In *sows* and *gilts*, flumethasone solutions or suspensions were ineffective when given between days 95 and 111 in dose levels ranging from 3–30 mg (65, 67), which is about 2–20 times the optimal therapeutic dose. In *women*, receiving up to 200 mg cortisone daily, from weeks 23 to 38 of gestation, or given very late during pregnancy (71a), and up to 30 (40) mg prednisolone daily throughout the pregnancy (71b), indications for premature or precocious induction of parturition were missing.

(*c*) *Mechanisms of action.—Cattle.* Possible explanations for the parturition-inducing corticoid effect are based on the following observations in treated animals: (*i*) A sharp drop of progesterone plasma levels, which precedes induction of labor when a corticoid effectively interrupts pregnancies (5, 18, 74). (*ii*) A short, dramatic rise in urinary estrogen excretion followed by an equally sharp drop (75). (*iii*) High corticoid blood levels seem to mimic a signal from the fetus. This interpretation is supported by the absence of the sharp rise in (endogenous) maternal corticoid blood levels observed about 2 days prior to normal parturition (27).

Corticoids seem to shut off the source of progesterone in the corpus luteum as well as in the adrenal; what direct effect they may have on the myometrium is unknown. Indirectly, the removal of the progesterone block at the myometrium and its sensitization by the available estrogens for oxytocic activities seem to create conditions mimicking closely the hormonal and autonomic neural conditions preceding and accompanying normal parturition in this species (76). This

TABLE 3. Fetal Condition and Response to Hormonal Induction of Parturition in Cattle During the Last Weeks of Gestation, around Calculated Term or in Delayed Gestation.

Condition of the Fetus	Response to Hormones, Applied to the Mother	
	CORTICOIDS	*ESTROGENS*
Alive, undisturbed	+++	+
Dead	−	+++
Hydroallantois	+++	−

also relates to the outburst in prolactin accompanying normal parturitions (77), which is also seen in all flumethasone-induced parturitions (18, 27).

This dramatic luteolytic effect of corticoids cannot be demonstrated in normally cycling heifers in which repeated administration of high doses of flumethasone in early and mid-cycle lowered plasma progesterone levels (78) but were without effect on cycle length (79); whereas the application of estrogens (80) at identical phases of the cycle exerts a clear luteolytic effect on the cyclic corpus luteum in heifers and cows. All these observations suggest the following hypothesis:

In cattle, the *corpus luteum of the cycle* and the corpus luteum of the *first trimester of pregnancy* are sensitive to the regressive force of estrogens, which are used widely to shorten cycles or to terminate early pregnancies. During the *second trimester of pregnancy*, the responsiveness of the corpus luteum to this estrogen effect diminishes. However, it is converted into a response to a combined effect of estrogens and corticoids. Therefore, estrogens and corticoids have to be applied in order to terminate pregnancy (5). This change in responsiveness seems to be a protective mechanism against the rising level of endogenous estrogen that begins during the second trimester. In the *third trimester*, increasing levels of estrogen seem to lead to a critical point: high estrogen levels and a short but critical rise in the blood corticoid levels interrupt the progesterone production process at all levels, including ovaries and adrenals (5, 27, 74). Normal parturition is induced by a trigger from the fetus—a rise in fetal and maternal corticoids. A prerequisite is normal estrogen production by the bovine placenta (75).

This hypothesis is substantiated by clinical observations. According to Vandeplassche (81), the corticoid effect in inducing parturition is confined to the presence of a living fetus; in case of a dead fetus, corticoids are inactive, but low doses of natural estrogens terminate these pregnancies rapidly and reliably. In cases of hydroallantois or hydroamnion in which estrogens clinically are without value, corticoids induce uncomplicated parturition within 48 hours and may save the fetus. In a case with hydrops allantois, treatment of the cow with 20 mg dexamethasone on day 212 resulted in parturition of a live fetus 41 hours later. The calf did not survive (82).

TABLE 4. Sources of Progesterone for Maintenance of Pregnancy in Ruminant Species Sensitive to Corticoid-Induced Parturition.

Species	Trimester of Gestation	Ovary C.l. Graviditatis	Placenta	Adrenal Cortex
Cattle	I	+	−	−
	II	+	−	+?
	III	+?	−	+
Sheep	I	+	−	−
	II	−	+	−
	III	−	+	−
Goat	I	+	−	−
	II	+	−	−
	III	+	−	−

Sheep. Contrary to the situation in cattle, progesterone in the pregnant ewe is supplied from the ovary in the first trimester, but from the placenta in the second and third trimester (Table 4). As shown by Liggins (40, 41) and Van Rensburg (12), corticoid derived from the fetal compartment, either directly by infusing corticoids into the fetal compartment or indirectly by ACTH stimulation of the fetus, resulted in premature parturition late in the second and throughout the third trimester. However, glucorticosteroids given to the maternal compartment even in large quantities are not effective until the final two or three weeks of the third trimester (Tables 1 & 2). According to Liggins et al (50), dexamethasone-induced parturition was accompanied by a fourfold increase of $PGF_{2\alpha}$ levels in uterine vein plasma. This seems to confirm the hypothesis by the same authors that prostaglandins, used so effectively in man to interrupt or terminate pregnancy at any time (83), may be last in the chain of events initiated by endogenous, fetal, or exogenous corticoids which result in expulsion of the fetus. In this respect the impressive luteolytic effect of prostaglandin $PGF_{2\alpha}$ observed in the ewe is of importance (84).

Goat. In the goat, the corpora lutea of pregnancy are the sole source of progesterone throughout gestation (12). The assumption is made that any pregnancy-terminating corticoid effect is mediated through pathways and mechanisms similar to those in cattle.

The Angora Goat abortion is a phenomenon only on the periphery to the mechanisms discussed here for corticoid-induced abortion. According to Van Rensburg (12) an abnormally low level of maternal adrenal function, coupled with some qualitative changes in adrenal steroid biosynthesis, seems to be the responsible mechanism. Physiological adaptation involved maternal and fetal adrenal hyperplasia, in order to assist the transfer of maternal nutrients to the fetus. Abortion is the consequence of the failure of this mechanism. Before

abortion, maternal plasma progesterone levels are abnormally high, and drop only in some animals (12). Adrenalectomy of the fetus, which causes indefinite prolongation of gestation in sheep, does not do so in the goat (12).

Horse. In the equine species, plasma progesterone levels decline from 15 to 0.5 ng/ml between the 4th and 6th months of gestation, signifying luteal regression (85). For the duration of the gestation period, the placenta appears to take over progesterone production (86) necessary for maintenance of pregnancy, with progesterone levels remaining less than 1 ng/ml plasma. The failure of corticoids to cause parturition suggests that the function of the placenta is not seriously altered (68).

Swine. No effects of corticoids in extremely large doses were seen in pregnant sows or gilts, although at the day of parturition a peak of plasma corticoids is recorded in the maternal plasma (78). Stable estrogen-progestin (pregnanediol) urinary excretion ratios for the last 4 days before parturition seem to call for an additional signal in this species for triggering parturition (87). The ability of the porcine species to metabolize corticoids (even suspensions) extremely rapidly is possibly the reason exogenous steroids do not exert a luteolytic effect on the sole source of progesterone, the corpora lutea.

Rabbits. Corticoids, given to rabbits during the second trimester, terminate gestation (88); corticoids inhibit trophoplast development and maturation by suppression of mitosis thus resulting in thinning and degeneration of the trophoplast. For induction of premature parturition, Kendall & Liggins (71) postulate an intermediate luteolytic effect of $PGF_{2\alpha}$ on the corpora lutea, an effect confirmed for this compound in pseudo-pregnant rabbits (89).

(*d*) *Counteractive mechanisms.—Cattle*. 100 mg progesterone given daily prevent precocious parturition caused by 10 (to 20) mg flumethasone (5, 90). At subsequent normal parturitions, occurrence of dystocia, stillbirth, and death of calves was above normal (90).

Sheep. 100 mg progesterone given to the mother were ineffective in overriding the pregnancy-terminating effect of dexamethasone or ACTH, if the latter was given directly to the fetus (50). Only 200 mg to the maternal compartment prevented parturition, although plasma and placental (cotyledonal) $PGF_{2\alpha}$ values were as high as during normal or induced parturition (50).

Goat. 20 mg progesterone into the maternal compartment rendered dexamethasone or ACTH infusions to the fetus ineffective (49).

3. Rationale for the Use of Corticoid-Induced Parturition in Animal Industry: Practical Experiences

(*a*) *Rationale.—Cattle*. Induction of parturition within a predictable period of days or hours is required in the dairy industry for better utilization of labor. This also would allow for veterinary supervision in situations in which a higher incidence of complications can be expected (twin pregnancies, cows with a known history of producing heavy calves, heifers and cows inseminated by bulls known to produce heavy calves). In most of these situations, precocious delivery of smaller calves would reduce dystocia problems, calf mortality, and the percentage

of stillborn calves. It would allow induction of premature or precocious parturition in cows with acute disease problems late in pregnancy, so the life of mother and fetus can be saved (26), and it would also allow termination of delayed pregnancies after day 290 (19, 26, 65).

In countries with a well defined and rather short breeding season, such as New Zealand and Australia, induction of parturition would be an important method for synchronizing parturitions in herds and to insure onset of postpartum cycling and breeding at the most desirable time.

Corticoid-induced termination of gestation in feedlot or dairy heifers found pregnant later than the 4th or 5th month of gestation, when estrogens alone are no longer effective in interrupting pregnancy, is of importance.

Sheep. In addition to the reasons mentioned for the management of induced parturition in cattle, a specific desire of the Karakul sheep industry seems to be close to fulfillment: delivery of lambs one week prior to term, at an age when they display the most desirable fur configuration and quality (14).

(*b*) *Effectiveness.—Cattle.* 95–100% precocious parturitions can be achieved with dexamethasone (1, 3, 6–9, 22–25, 30) and flumethasone (4–6, 19, 26, 65) at dosc levels shown in Table 2. For premature parturitions, the percentage seems to be somewhat lower (80–90%) (6, 65).

Sheep. 90–100% precocious parturitions result from flumethasone (13–16) and dexamethasone (2, 3, 20, 28, 29, 31, 32) at dose levels shown in Table 2, at a predictable time interval (1-3 days). With dexamethasone, some breed and timing differences were recorded: intervals between treatment and deliveries may vary with breeds, and ewes treated at 20:00 hours showed a tendency to lamb earlier and over a shorter period, if compared to ewes treated at 8:00 hours (32). Induced parturitions are remarkably fast and uncomplicated.

For the treatment of pregnancy toxemia in the ewe, corticoid treatment is widely used, although the reports of its effect are conflicting (91, 92). In Drost's experience (66), the standard recommended treatment for prepartum ketosis in the ewe with 20–25 mg dexamethasone does not result in induction of parturition or even signs of pending parturition. The metabolic disorder involved seems to make the ewe refractory to this corticoid effect.

(*c*) *Side effects.—Cattle.* In an extremely high percentage of cases, the *placenta is retained.* Practical experiences have shown that all attempts to remove the retained placenta by manipulation may cause metritis and pyometra. By far the best method is the immediate parenteral application of antibiotics and strict adherence to the advice not to try to loosen the placenta manually (6, 8, 65, 72). Its spontaneous delivery is observed in almost all cases within 8–10 days—mostly around calculated normal termination of the gestation period. This procedure assures, after spontaneous discharge of the fetal membranes, normal postpartum uterine involution and postpartum fertility (6, 8, 33, 65, 72). There seems to be a difference between investigators in the percentage of retained placentae seen, which might be related to the housing conditions of the treated animals; cows

confined in stanchions seem to have a higher rate of retention than those kept loose until parturition (19).

A clear correlation between the percentage of retained placentae and the interval between treatment and due term has been shown by Wagner & Evans (6). The closer to term an animal is induced to deliver, the lower is the chance for retention. The claim is made that retention of the placenta is peculiar for the action of so-called "short-acting" corticoids; "long-acting" preparations seem to show much less of this disturbance, approximately 20% only (72).

An ideal method of inducing parturition requires simultaneous parturition of fetus and placenta. Various investigators have used combinations of hormones to achieve this goal. The addition of diethylstilbestrol (DES)—the most commonly used estrogen in veterinary science—not only lacked the desired results, but created unexpected complications such as dystocia, and specifically the failure of the cervix to open (18, 65, 72). Grønborg-Pedersen (93) used natural estrogens successfully in 10 out of 13 animals for induction of parturition; however, the placenta was retained in 7 of those animals. If pregnant cows are ovariectomized at the beginning of the last trimester, no progesterone is necessary to maintain gestation, but parturition is hastened and the placenta is always retained. A daily substitution of 100 mg progesterone from days 248/264 to day 278 results in parturition at the calculated date and no placental retention (94). Based on these observations, the progestin, chlormadinone acetate (CAP) was used by Osinga et al (21) as well as by Adams (1) at dose levels for cycle synchronization (10 mg/day), beginning up to 8 days before the corticoid was injected: parturition was not prevented and delivery of the placenta was not influenced.

Stillbirth is not a problem in parturition induced by "short-acting" corticoids (see page 00 and Table 2). In cattle, the stillbirth rate was 2–3% (U.S.: 95) or 5.2% (U.K.: 96). Of 149 animals subjected to flumethasone treatment between days 240 and 270 of gestation, 80.2% responded with induced parturition; of those, 1.6% gave birth to a stillborn calf (65).

On the contrary, "long-acting" corticoids (see page 36) cause 31.4–43.9% of stillbirths (72). One of the reasons for this highly undesirable result might be the wide range of prematurely treated animals, spreading over most of the last trimester of the gestation period (72). From studies in sheep and goats it is clear that corticoids given to the maternal or fetal compartment early during the last trimester can cause fetal death (12). Extremely short gestations in cattle are associated in general with a higher frequency of stillborn calves (97, 98).

Onset of *milk production* is somewhat slower than normal; however, limited observations indicate that total production during the following lactation is not influenced (19, 21, 72). More research into this important aspect of the dairy industry's economy is warranted, as it is known from previous publications (99) that spontaneous abortion (or very early parturition) during the dry period may have a deleterious effect on the following lactation period. But milk production in itself may have an effect preventing the response of cows to otherwise parturition-inducing corticoid dose levels.

A method has been described to inhibit lactation in high-producing cows by

supplying 5 mg flumethasone (100). Although this is a dose level that may possibly endanger pregnancy in nonlactating animals, none was observed in more than 100 animals treated for the purpose of forced drying off, nor were there any signs of pending parturition noted (26). This report indicates an area that needs more detailed investigation. Since corticoids are essential for the process of milk production, a functional mammary gland may provide a buffer system absorbing excess corticoids.

Sheep. No undesirable side effects have been reported so far; viability of prematurely born lambs does not seem to impose problems (32). Since the placenta is always delivered simultaneously, no adverse effects on the postpartum period have been reported (13–16). In Karakul ewes, of three methods tested for induction of parturition (flumethasone, flumethasone plus DES, DES plus oxytocin), flumethasone alone had the least detrimental effect on ovarian function postpartum (16).

4. Natural Conditions Mimicking Corticoid-Induced Parturition

In cattle (101–104), sheep (105), goat (12), and man (106, 107), multiple gestations (twin, triplet, and quadruplet pregnancies) result in shortened gestation length, the shortening being proportional to the number of fetuses carried. Not only the increased intra-uterine volume, but also the combined effect of four or six rather than of two fetal adrenals may result in a situation similar to the corticoid-induced parturition. In cattle, twin or triplet pregnancies result in placenta retention (104). The large size of early born human fetuses has been already dealt with (62).

5. Sequence of Endocrine Events Preceding and Accompanying Parturition in Sheep and Man

Two similarities (among others) make a comparison between endocrine events preceding and accompanying parturition in sheep and man attractive: in both species, progesterone is supplied by the placenta during the 2nd and 3rd trimester of gestation; in both species, disturbances in the fetal adrenal development interfere with parturition at due term and prolong gestation.

In Tables 5 & 6, available information on the weeks before and the events during delivery are summarized for sheep and man. None of the many endocrine plasma and urinary excretion levels, in spite of their distinct patterns near term and during parturition, provide reliable clues for an answer to the unsolved question: which of these are responsible for triggering normal, spontaneous parturition in animal or man? Are there any clues that mechanisms similar to those discovered and described in detail in ruminants might have any bearing on endocrine dynamics near termination of the gestation period in man? The few in existence have been mentioned already. Thus multiple pregnancies in man shorten gestation length (106, 107) as in cattle and sheep. An atrophic adrenal cortex is often seen in anencephalic fetuses; their mothers exhibit a very low estriol (E_3) secretion rate (135), and their duration of gestation usually goes past term (58–64). In normal pregnancies ACTH given during the 2nd and 3rd tri-

TABLE 5. Hormonal Sequence of Events Preceding and Accompanying Normal Parturition in Sheep.

Endocrine Gland or Hormones	Maternal Compartment		Fetal Compartment	References		
	Before Parturition (a)	After Parturition (b)	Before Parturition (c)	(a)	(b)	(c)
Progesterone	Plasma levels (p.l.) decrease from day 120 (140) on.			49, 50, 108, 109, 110		
Estrogens	On day of parturition, 10-fold increase in p.l. of total unconjugated estrogens.	Drop to undetectable p.l.		49, 50, 110, 111		
Corticosteroids	p.l. declines from approx. day 130 on.		p.l. increases from day —10 on, reaching maximum on day —1/2.	48–50 54		48–50 54
STH			p.l. increases up to day —10, then sharp drop toward birth.			112
LTH	p.l. substantial increase in 3rd trimester.	Drop to baseline.		113		
ACTH	p.l. unchanged, but large fluctuations.	Unchanged	p.l. increased from day —15 on.	114		114
Vasopressin	p.l. unchanged, but large fluctuations.	Unchanged	p.l. increased toward term.	114		114
Prostaglandin $F_{2\alpha}$	Sharp increase in p.l. and in myometrium toward delivery.	Drop to undetectable p.l.		50, 110, 115	50, 115	
Thyroid	Placenta impermeable for maternal T_4.		Extremely high levels of FT_4 & T_4 decrease to normal levels from day —10 on.	49, 116		49, 116
Pancreas			Insulin production initiated late in 1st trimester of gestation; capacity to secrete insulin established only days before birth.			117

TABLE 6. Hormonal Sequence of Events Preceding and Accompanying Normal Parturition in Man.

Endocrine Gland or Hormones	Maternal Compartment: Before Parturition (a)	Maternal Compartment: After Parturition (b)	Fetal Compartment before Parturition (c)	References (a)	(b)	(c)
Progesterone	Plasma level (p.l.) decrease not observed and drop in p.l. not a prerequisite for initiation of labor.	During parturition: slow decrease in p.l. (at full opening of the cervix only 20% decrease.)		118 119	118 119	
Pregnanediol	Higher p.l. than progesterone. Ratio pregnanediol to progesterone increases before and during parturition.			118	118	
Estrogens: Estrone $= E_1$ Estradiol $= E_2$ Estriol $= E_3$	Uniform urinary excretion pattern of E_1, E_2, & E_3: after steady increase, leveling off from week 24–26 on; sharp increase during last 3–4 weeks. E_3: quantitatively the most important estrogen.	Sharp drop in p.l. and urinary excretion immediately p.p.		119 120	119 120	
Androgens: DHAS	p.l.: constant drop during pregnancy, reaches its minimum late 3rd trimester.	p.l. rises sharply during parturition but drops again in the days p.p.	At parturition: umbilical cord, vein and artery levels within normal range.	121	121	121
DHA	p.l.: dropping to a minimum, below normal, at week 37.	p.l.: sharp rise during parturition but drop below gestation minimum p.p.	At parturition: umbilical vein and artery low. p.l. resemble mother's p.p. minimum.	121	121	121

Testosterone	p.l. climbs continuously during gestation, reaches maximum close to term.	p.l. during parturition unchanged high; within 3 days p.p. return to normal p.l.	At parturition: umbilical vein and artery p.l. are within the normal range.	121	121	121
Δ_4-Androstene-dione	p.l. climbs continuously during gestation, reaches maximum close to term.	p.l. during parturition unchanged high: within 3 days p.p. return to normal p.l.	At parturition: umbilical vein p.l. higher than normal, artery levels high but within normal range.	121	121	121
Cortisol	p.l. of cortisol and transcortin rise progressively during gestation toward term: resulting in little or no increase in free *cortisol*. Significant increase in free, biol. active corticosteroid concentrations during entire gestation.		At parturition: p.l. in the umbilical cord similar to the mother's p.l.	122 123		122
Prostaglandins		p.l. of F2 α become measurable just before parturition peak values are recorded during contraction in spontaneous labor.			119	

TABLE 6. Hormonal Sequences of Events Preceding and Accompanying Normal Parturition in Man.

Endocrine Gland or Hormones	Maternal Compartment: Before Parturition (a)	Maternal Compartment: After Parturition (b)	Fetal Compartment before Parturition (c)	References (a)	(b)	(c)
Aldosterone	Secretion rate increased continuously and substantially during gestation, with peak values weeks 38–40.			124		
HCG	If determined by the ovarian hypercenia test in rats, a 2nd peak in p.l. is observed close to term.	Fast disappearance from maternal and fetal blood with a remarkable change in halflife: 3 hours halflife for the 1st two hours p.p., 13 hours for the next 22 hours, and 23 hours for the days thereafter.		125	126	126
HPL	p.l. increase toward term.	p.l. maximum during parturition.	Only 0.3% of the maternal p.l. are found in fetal plasma.	127	127	127
Renin	A second (minor) secretion peak is recorded toward term.			124		
Insulin	Pancreatic β-cell hyperfunction, starting at weeks 10–12, reaches maximum by delivery time.		p.l. lower than and not related to the p.l. of mother.	128		128
Thyroid	Estrogens push production of TBP, which in turn rises T_4 circulation, but not free T_4	At term, mother's thyroid enlarged but functions normally; T_3 and T_4 are normal; TBP and PBI are derated, resin uptake is reduced.	At term, fetal thyroid normal; T_3 and T_4 are normal; TBP and PBI are elevated; resin uptake is reduced.	129	129	129

Prolactin	Steady rise during pregnancy toward maximum (ca. 30 times base levels) at term.	Return to baseline levels within 96 hours.		130	130	
Growth hormone of:	No increase toward term; no increase during delivery.	Rapid decreases during hours 2–4 p.p. to 20–50% of starting values. Slow start: subnormal for 7 days.	No increase toward term.			131
(a) pituitary			Rapid decrease during hours 2–4 p.p. to 4–40% of starting values.	131 132	133	133
(b) chorionic origin			p.l. extremely low, but high concentrations in meconium.			131 132
TSH		After initial drops, slow rises 12–24 hours p.p.	From a high baseline immediately p.p., p.l. increase up to 6 times during 2nd hour p.p., and decrease slowly afterwards.		126	126
Oxytocin and Vasopressin	Rare in maternal blood during delivery.		High levels in umbilical vein and highest levels in umbilical artery.	134		134

Legend:

DHAS = dehydroandrostenedione sulfate
DHA = dehydroandrostenedione
HCG = human chorionic gonadotropin
HPL = human placental lactogen
TBP = thyroxin-binding protein
PBI = protein-bound iodine

mester increases maternal urinary estrogen output (136), and dexamethasone reduces estrogen (E_3) excretion (137, 138). This dexamethasone effect on E_3 is inconsistent in mothers with anencephalic fetuses (139).

The same biochemical deficiency is observed in adrenal dysfunction in sheep fetuses caused by *Veratrum californicum* (46). Since the fetal adrenals, normally a large source of estrogens (mostly estriol = E_3) precursors, are either not functioning or not sufficiently functioning, a compensatory hypertrophy of the fetal ovaries is observed temporarily around term. These tenfold enlarged ovaries are stimulated by what seems to be a placental gonadotropin to produce large quantities of estrogens (estrone, estradiol, and estriol) (46). These estrogens cause signs of pending parturition (edema of vulva and mammary glands, relaxation of pelvic ligaments), but fail to induce parturition (46).

Present insight into fetal adrenal development towards term in sheep can be summarized as follows. Until shortly before normal parturition, C_{21} steroid 11β-hydroxylation activities are low, but C_{19} steroid 11β-hydroxylation activities are high. As a result, 11-deoxycortisol is the major 17-hydroxylated steroid produced in fetal sheep (47). This compound is inactive if infused in utero around day 110 (50–100 mg for 7–8 days) to induce parturition (47), while cortisol at the same time is active in this respect (47). ACTH from either exogenous or endogenous sources stimulates C_{21}-steroid 11β-hydroxylation. The ensuing cortisol and corticosterone blood levels are prerequisites for the events leading to parturition. Another prerequisite is the fetal adrenal's capability, under the stimulation of a placental gonadotropin, to produce 3β-hydroxy-5ene steroids, precursors for the estrogen production of the placenta; with the 16-hydroxylation liver system as a third partner in the maternal-fetal unit preparing for parturition (46, 140). Close to parturition, the adrenals mature and reduce these activities in favor of cortisol/corticosterone production (46, 47). In man, the placenta produces estrogens without fetal participation (139).

In Tables 5 and 6, summarizing the hormonal events around parturition in man and sheep, oxytocin has been omitted in sheep, and only fetal values are given in man. Research in animal and man during the last two decades has shown that oxytocin does not initiate labor (141–144), whereas it is an essential factor for the orderly sequence of events during and after delivery. Its release, during the stage of cervical and vaginal stretching by the fetal forehead and skull, accelerates the expulsion of the fetus, thus preventing prolonged asphyxia due to compression of the umbilical cord and by the partial separation of the placenta (143).

The role of oxytocin for induction of labor has been overestimated in the past (141–145). Today it is clear that, unlike the oxytocin-initiated milk ejection, there is no sole oxytocin-initiated child ejection (144). Initiation of parturition is a process for which species or groups of species may have developed specific triggers. All may result in similar hormonal and biochemical chain reactions that assure expulsion of fetus, placenta, and uterine involution.

But all this insight has not revealed what really triggers the endocrine preparations and adjustments in the fetal compartment toward term. Since undisturbed hypothalamic functions are essential, the notion that in the sheep, maturation of

the hypothalamic thermoreceptors takes place approximately 10 days before term, could be of importance (49, 116). As a result, the fetus becomes aware of its thermal status: before the last week of gestation, the fetus is hyperthyroid (49, 116). Mechanisms of this nature may play a role in the initiation of parturition (49, 116).

6. General Discussion and Conclusion

In four species, of which three are ruminants with different sources of progesterone for maintaining pregnancy in the second and third trimester (Table 4), adrenal corticoids from the fetus seem to play an important part in induction of normal parturition. Glucocorticoids, if given to the mother, specifically at the end of the last trimester, mimic this effect with a predictable interval to parturition. The economic value of this discovery to the cattle industry is considerable, provided proper management of the side effects of retained placenta and stillbirth can be overcome.

The corticoid effect on progesterone plasma and estrogen levels seems to support the so-called progesterone withdrawal theory for the induction of normal parturition. This theory may have validity for cattle, as shown in our own studies (90), but does not always hold up in sheep (50) and is at least doubtful in pigs and horses (65). It is based on the assumption of removal of the so-called progesterone block for oxytocin on the myometrium (145–147), together with increasing sensitivity of the myometrium to oxytocin due to increasing levels of estrogen (111, 140).

More likely is the possibility that the endocrine changes trigger release of prostaglandins in much the same way as occur at the end of the estrous cycle in sheep (148, 149). Prostaglandins are luteolysins as well as inducers of oxytocin-like contraction of the myometrium (150).

Species differences in the mechanisms initiating and executing parturition are becoming obvious and require study of conditions in each species separately. Recent insights into mechanisms of mammalian parturition indicate that generalizations are no longer acceptable. This holds even for intriguing concepts such as that of Csapo (151) on the regulatory interplay of progesterone and prostaglandin $F_{2\alpha}$ in the control of the pregnant uterus at term; although one might agree that in most species the pregnant uterus is an intrinsically active organ, which after progesterone withdrawal recovers from its anesthesized status and starts to expell its content by itself.

Blood levels, on which so many interpretations are based, reflect not only changes in production and release, but also changes in metabolic clearance rate. Contrary to the in vivo situation in cattle, where the corpus luteum seems to become unimportant as a progesterone source during the 3rd trimester of gestation (152), its capacity to produce progesterone in vitro late in pregnancy is unimpaired (153).

In the pregnant guinea pig, the metabolic clearance rate of progesterone decreases sharply between days 15 and 20 after mating, and for the remainder of the pregnancy it is less than 10% of the value found in nonpregnant animals.

This decrease depends on the presence of viable fetuses (154). The progesterone-conserving mechanism in the guinea pig is in contrast to the increased progesterone synthesis required in other species for the maintenance of gestation, for example in man (154).

Are prostaglandins only luteolysins and myometrial stimulators, or do they act also as hemodynamic regulators, reducing blood flow toward the fetus or within the fetus (155)? What is their effect on steroid receptors in the uterus? In many instances estrogen priming seems to be necessary to make these receptors "attractive" to progesterone (156); in the sheep and the cow progesterone-priming only allows estrogens during heat to exert their effects on the receptor sites fully. Toward term in the rat the number of binding sites for progesterone diminishes, and close to term their concentration is very low (157). Does this result from an estrogen dominance, or a progesterone replacement by prostaglandins, or are the latter able to free receptors for estrogens? It seems to be important that low progesterone tissue concentration, essential for normal as well as induced parturition, may result not only from lowered plasma progesterone concentrations, but also from changes in cytoplasmic "receptor" protein. Finally, corticoids and estrogens are known to be catatoxic steroids. Catatoxic steroids increase metabolic rate and effectiveness for progesterone elimination by the liver and may contribute also by this mechanism to an endogenous milieu ready for delivery of the fetus (158).

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